9. (Amended) A method for treatment of a human condition or disease requiring or benefitting from a central nervous system stimulant comprising administering to said human an effective amount of a pharmaceutical composition comprising (R,R')(R,S')-amphetaminil sulfate or another pharmaceutically-acceptable salt thereof, substantially free of (S,R')(S,S')-amphetaminil.

REMARKS

The Rejections Under 35 USC Section 103(a)

In response to the Examiner's rejection of claims 1-8 as unpatentable in view of US Pat. No. 5,462,746 (Wolter) and of claims 9-22 over US Pat. No. 6,217,904 (Midha) in view of Wolter, Applicants strongly contend that: i) the properties of the enantiomer, specifically its lomototor activity and stereotypy profiles, are unexpected; and ii) separation of the enantiomers is unexpectedly difficult and that their use, rather than the use of the racemate, in the compositions of the aforementioned references, is non-obvious, and that therefore the invention is accordingly non-obvious and patentable over the prior art.

In response to page 3 of the Office Action, in which the Examiner states that "the data showing greater activity appears to be expected absent further clarification or arguments of superior results", Applicants wish to specifically point out that there are unexpected and significant differences between the racemate and the isolated enantiomer in terms of its locomotor activity profile which Applicants wish the Examiner to note. As Example 4 clearly illustrates, the "pure R" amphetaminil has a locomotor activity profile which is more similar to amphetamine rather than the racemate and has

a lower stereotypy profile as evidenced by the Figures; in fact, the locomotor activity-to-stereotypy ratio is over 100% greater for pure R amphetaminil compared to the racemate (for a detailed discussion, see table on page 33 of specification, and compare Fig. 1A-C with Fig. 3A-C and 4A-C). Additionally, as noted on page 4 of the specification, use of the pure R amphetaminil is suitable for any condition or disease in which racemic amphetaminil or amphetamine (more specifically D-amphetamine) have been used. Page 4 goes on to explain that a significant and non-obvious advantage of the pure-R enatiomer lies in the fact that

> *"less activation or promotion of stereotypic behavior is elicited by this composition than by racemic amphetaminil, and therefore may be less likely to exhibit or exacerbate movement disorders in patients in which this compound is administered. This is particularly beneficial to the treatment of Parkinson's disease and individuals with ADHD who exhibit tics".*

This 100% greater locomotor activity-to-stereotypy ratio for pure R amphetaminil compared to the racemate is an unexpected result that certainly would not have been obvious to one ordinarily skilled in the art.

Furthermore, additional evidence of the non-obviousness of modifying the compositions of Wolter or Midha to contain one isomer over the other is the difficulty of the separation of the enantiomers of the racemate. As discussed on page 9 of the specification, amphetaminil possesses two dissymetric centers. The compound of the invention is the R form at the first or amphetamine-like dissymetric center and is racemic at the second, or benzenacetonitrile-like center.

As described on pages 10-11 of the specification, separation of the enantiomers with any measurable degree of success, was only feasible at the first chiral center and by conversion to the sulfate salt of the of amphetaminil, because the sulfate salt minimizes degradation of the compound which would otherwise occur, making the separation difficult or impossible. As stated in the specification,

> *"the invention is also directed to a facile, non-obvious means for stabilizing the enantiomers by converting the products of the synthetic reaction at the stage of formation of amphetaminil into sulfate salts."*

Example 1, page 18 et seq. provides detailed discussion of the problems of isolation of the enantiomers. As page 19 explains, attempts at recrystallization of the purified isomers using a variety of solvents were unsuccessful, with no separation achieved and almost total breakdown for all isomers. Attempts at chromatographic purification of the (+) and (-) amphetaminil free bases were similarly unsuccessful. Only when the (+) and (-) amphetmanils were converted almost immediately into the sulfate salt was the purity and yield acceptable (as measured by gas chromatography and NMR analysis). This difficulty of separation of the enantiomers is strong support for Applicant's assertion that it would have been non-obvious to modify the compositions of Wolter or Midha to contain one isomer over the other, since the achievement of pure isomers is unexpectedly difficult, must be done at the first chiral center, and requires immediate conversion to the sulfate salt.

The Rejections Under 35 USC Section 112, first paragraph

In order to overcome the Examiner's rejection of claims 9-22 under 35 USC Section

112, first paragraph (lack of enablement) Applicants have accepted the Examiner's suggestion and amended claim 9 so that it no longer contains the word "prophylaxis" and is now more specifically directed only to a method for treatment. Applicants accordingly request reconsideration of the claim 9-22 and withdrawl of the rejection.

Fees

No fees are believed to be required for this Response and Amendment. However, should any fees be necessitated hereby, authorization is hereby given to charge Deposit Account no. 11-1153 for any underpayment.

CONCLUSION

Entry of the foregoing remarks into the record of the above identified application is respectfully requested. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosure: Version with Markings to Show Changes

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Vela Pharmaceuticals

SERIAL NO. : 09/992,235 EXAMINER : Delacroix Muirhei, Cybille

FILED : November 6, 2001 ART UNIT : 1614

FOR : (R,S'),(R,R')-AMPHETAMINIL, COMPOSITIONS AND USES THEREOF

AMENDMENT AND RESPONSE
VERSION WITH MARKINGS TO SHOW CHANGES

9. (Amended) A method for [prophylaxis or] treatment of a human condition or disease requiring or benefitting from a central nervous system stimulant comprising administering to said human an effective amount of a pharmaceutical composition comprising (R,R')(R,S')-amphetaminil sulfate or another pharmaceutically-acceptable salt thereof, substantially free of (S,R')(S,S')-amphetaminil.